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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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09/092,296 06/05/98 BILLING-MEDEL

P 6104.US.01

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HM22/1108

EXAMINER

BURKE, J

ART UNIT	PAPER NUMBER
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1642

11

DATE MAILED:

11/08/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

# Office Action Summary

Application No.  
09/092,296

Applicant(s)

Billings-medel et al

Examiner

Julie E. Burke, (Reeves), Ph.D.

Group Art Unit

1642

☒ Responsive to communication(s) filed on 17 Sep 1999

☐ This action is FINAL.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire three month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

## Disposition of Claims

☒ Claim(s) 1-14 and 16-33

is/are pending in the application.

Of the above, claim(s) 7-10 and 13

is/are withdrawn from consideration.

☒ Claim(s) 26

is/are allowed.

☒ Claim(s) 1-6, 11, 12, 14, 16-25, and 27-33

is/are rejected.

☐ Claim(s) \_\_\_\_\_

is/are objected to.

☐ Claims \_\_\_\_\_

are subject to restriction or election requirement.

## Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on \_\_\_\_\_ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on \_\_\_\_\_ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

## Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some\* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) \_\_\_\_\_

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

\*Certified copies not received: \_\_\_\_\_

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

## Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). \_\_\_\_\_

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

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### **DETAILED ACTION**

1. Claim 5 has been canceled. Claims 1, 4, 5, 11 and 12 have been amended. Claims 16-33 have been added. Claims 1-14, 16-33 are pending. Claims 7-10 and 13 are withdrawn from examination as being directed to non-elected inventions. Claims 1-6, 11-12, 14, 16-33 are under examination. It is noted that claim 14 is under examination as it is directed to polynucleotides.
2. The text of those sections of Title 35, U.S.C. Code not included in this Office Action can be found in a prior Office Action.
3. The following contains some NEW GROUNDS of rejection.
4. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention (products and not methods) to which the claims are directed.

### ***Priority***

5. Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged. However, the provisional application upon which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for claims 1-6, 11-12, and 15 of this application for the reasons set forth in the previous Office Action. The response set forth on page 8 has been considered carefully but is deemed not to be persuasive. The response argues that nucleotide 5-419 of SEQ ID NO: 7 are the same as residues 1-415 in SEQ ID NO: 9 of the provisional application. This is not persuasive because the claims are not limited to the portions of the sequences which are argued to be identical. Applicant is reminded that the claims define the subject matter of his invention and that the specification cannot be relied upon to read limitations into the claims.

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Arguments presented that rely on particular distinguishing features are not persuasive where those features are not recited in the claims. Claims to SEQ ID NOS: 1-7 of the instant application are therefore not supported by provisional application 60/048,810, and the priority date of the instant application is the June 5, 1998 filing date.

***Claim Rejections - 35 U.S.C. § 101***

6. Claim 14 stands rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter for the reasons set forth in the previous Office Action.

The response set forth on page 7 has been considered carefully but is deemed not to be persuasive. The response argues that applicants have assumed, in view of the typographical error of the previous examiner, that claim 14 is not pending and that claim 14 is directed to a polypeptide. Upon review of claim 14, it is determined that claim 14 is properly under examination. The Examiner apologizes for any inadvertent inconvenience by the confusion of the previous Office action. Thus the rejection is made again and maintained. Amending the claim to recite the purified polynucleotide, or similar language as supported by the specification as originally filed, may be sufficient to obviate this rejection.

dnf

***Claim Rejections - 35 U.S.C. § 112***

7. Claim 14 stands rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for the reasons set forth in the previous Office Action.

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a. The response set forth on page 7 and 9-12 has been considered carefully but is deemed not to be persuasive. The response argues that applicants have assumed, in view of the typographical error of the previous examiner, that claim 14 is not pending and that claim 14 is directed to a polypeptide. Upon review of claim 14, and as set forth above, it is determined that claim 14 is properly under examination. Thus the rejection is made again and maintained.

Removing the limitation "% identity" would obviate this rejection.

8. The following are NEW GROUNDS of rejection.

9. Claims 1-4, 22-25, 12, 30-33 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims have been amended to recite "polynucleotide that specifically binds to a polynucleotide sequence". The response states that support for this amendment is found on page 20 line 27 to page 21 line 7; page 21, lines 24-36, page 22, lines 11-26; page 24; and page 6, line 4 to page 7, line 32. Upon careful review of this text, the examiner has been unable to find adequate support for the newly added limitation. The text does not support the concept of polynucleotide (molecule) which specifically bind to sequences (information) or even for polynucleotides which specifically bind to polynucleotides. Nucleic acid typically hybridize to other nucleic acids. The term of DNA as a specific binding partner in the specification appear to refer to DNA as an antigen for an antibody and not DNA

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which binds (hybridizes?) To another DNA molecule. Applicant is required to either point to where the specification provides support for the phrase or to remove it from the claims.

10. Claims 5-6, 16-18 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The newly amended claims now recite an open reading frame of "at least 5 amino acids", "at least 8 amino acids", and "at least 10 amino acids". The response argues that support for this limitation can be found on page 17, lines 13-16. This argument is not persuasive because the text found on this page discloses that an open reading frame comprises the ranges of "at least about 3-5 amino acids", "at least about eight to ten amino acids" and "at least about 15-20 amino acids". The narrower limitation inserted into the claim is not supported by the broader teachings in the specification. Applicant is required to either point to where the specification provides support for the phrase or to remove it from the claims.

11. Claims 11, 22-25, 30-33 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The newly amended claims now recite a polynucleotide of "at least about 10 nucleotides", "at least about 12 nucleotides", "at least about 15 nucleotides" or "at least about 20 nucleotides". The response argues that support for this limitation can be found on page 18, lines 23-29 and page 14, lines 8-34. This argument is not persuasive because the text

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found on this page discloses that a polynucleotide comprises the ranges of "at least about 10-12 nucleotides" or "at least about 15-20 nucleotides". The narrower limitation inserted into the claim is not supported by the broader teachings in the specification. Applicant is required to either point to where the specification provides support for the phrase or to remove it from the claims.

12. Claims 20-21, 28-39 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The newly amended claims now recite an epitope of "at least 8 amino acids" or "at least 10 amino acids". The response argues that support for this limitation can be found on page 18, lines 23-29 and page 14, lines 8-34. This argument is not persuasive because the text found on this page discloses that an epitope consists of the ranges comprising "at least 8 to 10 amino acids". The narrower limitation inserted into the claim is not supported by the broader teachings in the specification. Applicant is required to either point to where the specification provides support for the phrase or to remove it from the claims.

13. Claims 1-6, 11-12, 14, 16-25, 27-33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 1-4 and 22-25 are indefinite for reciting "Polynucleotide sequence" as it not clear how "sequences" could specifically bind to a polynucleotide (molecule). The term

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“sequence” refers to information describing the nucleic acid or amino acid sequence. Information is not a chemical structure, therefore, it is not clear how “sequences” can bind to nucleic acid molecules. Replacing this term with polynucleotide, DNA, RNA or polypeptide, as appropriate, would obviate this rejection.

b. Claims 1-4, 22-25, 11 and 12 are indefinite for reciting “complement”. The term “complement” can mean a polynucleotide complementary to a small region of a given DNA or alternatively complementing the entire region, with a loop structure in the middle of the full length sequence or alternatively, complementing the entire region with no loop structure present. Accordingly, as written, it is impossible for one skilled in the art to determine the metes and bounds of the claims. Replacing the term “complement” with the phrase “full complement” or some other language that is supported by the specification as originally filed, would obviate this rejection.

c. Claims 1-4, 22-25, 12, 30-33 are indefinite for reciting “specifically binds to”. The claims fail to include under what conditions the polynucleotide specifically binds to another polynucleotide. As written, it is impossible for one skilled in the art to determine the metes and bounds of the claims.

d. Claims 4, 11, 12, 19-21, 27-29 are indefinite for reciting “epitope”. An epitope is defined as a portion of a molecule bound by a particular antibody. Because the claims are silent as to the antibody which binds the epitope, it is impossible for one skilled in the art to determine the metes and bounds of the claims.



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e. Claims 5-6, 16-18 are indefinite for reciting “a recombinant expression system” because it is not clear whether these claims are reciting a product, a kit or a method/process. *Main*  
Additionally the claims are indefinite for reciting an open reading frame operably linked to a *16-18*  
control sequence. As set forth above, sequence is information and it is not clear how an open reading frame (molecule) can be linked to information. Amending the claim to recite a promoter or enhancer or other such language as supported by the specification as originally filed may be sufficient to obviate this portion of the rejection.

f. Claims 11, 19-21 are indefinite for reciting “cell transformed with a nucleic acid sequence” because sequence is information and it is not clear how a cell can be transfected with information.

g. Claim 14 is indefinite for reciting a “gene” because it is not clear what structural features are encompassed by the claims. According to Genes IV (Lewin et al, Oxford University Press, page 810, 1990), a gene is defined as “the segment of DNA involved in producing a polypeptide chain; it includes regions preceding and following the coding regions (leader and trailer) as well as intervening sequences (introns) between individual coding segments (exons).” From the teachings of the specification, however, the nucleic acid sequences introducing antigens or marker elements appear limited to the specific coding regions, and do not include expression control elements that fall under the definition of a gene. Accordingly, the claims are indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 14 is also indefinite for reciting “fragment” because it is not clear how small

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fragments is encompassed by the claim-- a single nucleotide or an atom from a nucleotide? As written, it is impossible for one skilled in the art to determine the metes and bounds of the claims.

14. Claims 1-6, 11-12, 14, 16-18, 22-25 and 30-33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for polynucleotides comprising or consisting of SEQ ID NO: 1, 2, 3, or 7, does not reasonably provide enablement for the various fragments, genes, complements and polynucleotides which specifically bind to the various polynucleotides, as claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. .

a. Factors to be considered in determining whether undue experimentation is required, are summarized in *Ex parte Forman*, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

b. The claims broadly recite polynucleotides which comprises a polynucleotide that specifically binds to a polynucleotide sequence selected from the group consisting of SEQ ID NO: 1, 2, 3 and complements thereof; wherein the sequence encodes an epitope. Also recited are expression system comprising nucleic acid sequences derived from a polynucleotide selected from the group consisting of SEQ ID NO: 1, 2, 3, and nucleotides 51-284 of SEQ ID NO: 7, wherein

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the polynucleotide encodes an epitope. Also, the claims recite polynucleotides encoding open reading frame fragments and epitopes as small as 5, 8, 10, 15 amino acids. Claim 14 recites a gene or fragment thereof. Also the claims recite polynucleotides fragments as small as 10, 12, 15 or 20 nucleotides in length.

c. “Specifically binding polynucleotides” or “complements” or “fragments” or “genes or polynucleotides “derived from” may include various mutations, deletions, insertions and fusion proteins of the encoded protein. Since the specification has not identified which amino acids or nucleic acid sequences are critical or essential characteristics of the LS147 protein encoded by SEQ ID NO 1, 2, 3 or 7 there is a lack of sufficient guidance to determine which amino acids substitutions or protein domain alterations or mRNA sequence changes could be made without altering the fundamental characteristics of the LS147 antigen or LS147 epitope and there are insufficient working examples of any such variants. Since the state of the art of protein modification suggests that the effects of sequence alterations are unpredictable and since the specification provides no guidance as to which changes would result in an active protein or viable LS147 antigen or epitope, undue experimentation would be required to determine which specifically binding DNAs or which complementary DNAs or which genes or fragments or which derived polynucleotides would encode an authentic LS147 mRNA or LS147 protein with all its identifying characteristics.

d. Moreover, the specification fails to recite under what conditions the claimed DNA would anneal to the LS147 DNA/ mRNA. Under low stringency conditions, it would be expected

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that a wide variety of unrelated DNA molecules would be able to anneal to the LS147 mRNA. The specification is silent concerning the washing conditions, molarity of the salt, degree of temperature and length of the incubations that result in the hybridization. In absence of such guidance and/or working examples, one skilled in the art would reasonably conclude that a large number of DNA molecules would be able to hybridize, however, the specification has not taught how all the hybridizing or specifically binding molecules would be LS147 DNAs, that express the claimed mRNAs or encode the claimed proteins.

e. As taught in Greenspan et al (Nature Biotechnology 7:936-937 (1999)) defining epitopes is not as easy as it seems (page 937). Epitopes have been defined in terms of the spacial organization of residues that make contact with a ligand and the structural characterization of the molecular interface for the binding of the molecules to define the epitope boundaries (page 937 middle of page). The epitope defined in this manner will likely include residues that contact the ligand but are energetically neutral or even destabilizing to binding. "In addition, a priori it will not include any residue that makes no contact with a ligand but whose substitution may profoundly effect ligand recognition through influence on the stability of the free form of the macromolecule, or participation in long-range allosteric effects". "Even when the residues making contacts with ligands are known with certainty, say from the crystal structure of the complex, the question remains with regard to the energetic involvement of each residue (page 936 right column, first paragraph). Therefore, "amino acids should be recognized to have multiple ways of contributing to a noncovalent interaction" (page 937, middle of page). As evidenced by

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Greenspan et al a number of factors not primarily related to the contours of the contacts of the molecules contribute to the free energy change, sometimes profoundly.

Further, Geysen et al (Proc Natl Acad Sci USA Vol 81 3998-4002, 7/84) demonstrate that single amino acid differences in pentamer peptides are critical for antibody binding and that not all amino acids are equally important (page 4001, col 2, first full paragraph and Table 1, page 4000).

f. Further, the specification fails to teach what mutations or amino acid substitutions/insertions are capable of maintaining the three dimensional structure of an epitope. The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with reasonable expectation of success are limited. Certain positions in the sequence are critical to the three-dimensional structure/function relationship, and these regions can tolerate only conservative substitutions or no substitutions. See Bowie et al (Science, 247:1306-1310, 1990, p. 1306, col.2). Accordingly, one skilled in the art would reasonable conclude that it would be equally unpredictable to determine which polynucleotide molecules would encode the polypeptides of appropriate structure and/or function.

g. Therefore, in view of the speculative nature of the invention, the lack of predictability of the prior art, the breadth of the claims and the insufficient guidance, teachings and working examples, it would require undue experimentation for one skilled in the art to make and

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use the invention as claimed. Amending the claims to recite polynucleotides comprising or consisting of SEQ ID NO: 1, 2, 3, or 7 would obviate this rejection.

***Claim Rejections - 35 U.S.C. § 101***

15. 35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

16. Claims 5-6, 16-18 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claims recite a recombinant expression system, however, it is not clear whether the claimed "system" is a product, a kit or a method.

***Claim Rejections - 35 U.S.C. § 102***

17. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

18. Claims 1-4, 22-25 and 12, 30-33 are rejected under 35 U.S.C. 102(b) as being anticipated by Adams et al (Nature Vol 377 3-174 1995), as evidenced by the attached computer sequence alignments. The claims are drawn to a complements of purified polynucleotide specifically binds

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to a polynucleotides sequence selected from the group consisting of SEQ ID NO:1, 3. Claims 2 and 3 are further drawn to purified polynucleotides produced by recombinant or synthetic techniques, respectively. Claim 4 further limits claim 1 wherein the claimed sequence encodes at least one epitope. Claims 22-25 recite polynucleotide fragments of at least about 10, 12, 15 or 20 nucleotides. Claims 30-33 recite fragments of at least about 10, 12, 15 or 20 polynucleotides.

a. Adams et al teach a polynucleotide sequence that includes the claimed sequences that would be complements of SEQ ID NO: 1 or 3, as evidenced by the attached computer sequence alignments. The sequences taught by Adams et al would complement SEQ ID NO: 1 or 3.

b. Claims 2 and 3 are drawn to a polynucleotide produced by recombinant or synthetic techniques. The method in which the polynucleotides were produced is immaterial to their patentability. "Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 227 USPQ 964, 966 (Fed. Cir. 1985). See also MPEP 2113. Therefore, claims 2 and 3 are also rejected over Hillier et al under 35 U.S.C. 102(b).

c. Claim 4 is further drawn to polynucleotides that encode at least one epitope. For the purposes of this rejection, an epitope is considered as generally and well known to one of

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ordinary skill in the art as an amino acid sequence of a protein, usually 5-6 amino acids in length, that binds to an antibody. Considering the substantial sequence identity of Adams et al to SEQ ID NO:1, or 3, taken in view of the breadth of the claims, there is at least one epitope encoded by the sequence taught by Adams et al. Furthermore, the fragments or complements recited in claim 12, 22-25 encompass the polynucleotides of Adams et al.

19. Claims 1-6, 22-25, 11, 12, 16-18, 30-33 are rejected under 35 U.S.C. 102(e) as being anticipated by Kuroda et al (US Patent 5,773,688 filed 7 Apr 1995), as evidenced by the attached computer sequence alignments. The claims recite fragments and complements as discussed above which specifically bind to SEQ ID NO: 2.

a. The claims 1-4, 22-25, 12, 30-33 have been described above. Claims 5-6, 16-18 recite an expression system and cell comprising a nucleic acid sequence derived from SEQ ID NO: 2 which encodes an epitope. Kurado et al teach polynucleotide molecules which encompass the fragments, derivatives, and complements recited in the claims as evidenced by the attached computer sequence alignments.

20. The rejection of Claims 1-4 and 12 under 35 U.S.C. 102(b) as being anticipated by Hillier et al (GenBank Accession T94049) is withdrawn in view of the amendment(s) to the claims.

21. The rejection of Claims 1-3 under 35 U.S.C. 102(b) as being anticipated by NEB catalog is withdrawn in view of the amendment(s) to the claims.



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***Claim Rejections - 35 U.S.C. § 103***

22. The rejection of Claims 5, 6, and 11 under 35 U.S.C. 103(a) as being unpatentable over Hillier et al (GenBank Accession T94049) in view of Ausubel et al. is withdrawn in view of the amendment(s) to the claims.

***Conclusion***

23. Claim 26 is free of the prior art because the prior art because the prior art fails to teach or fairly suggest a polynucleotide consisting of 51-284 of SEQ ID NO: 7. Claim 26 is in condition for allowance.

24. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Julie E. Burke, née Reeves, Ph.D, whose telephone number is (703) 308-7553. The examiner can normally be reached on Monday through Friday from 8:00 am to 5:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paula Hutzell, can be reached on (703) 308-4310. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

25. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal

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Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Respectfully,

A handwritten signature in cursive script, appearing to read "J. Burke".

Julie E. Burke, née Reeves, Ph.D.

Primary Patent Examiner

(703) 308-7553

**JULIE BURKE  
PRIMARY EXAMINER**